COMMUNICATION

A facile and regioselective multicomponent synthesis of chiral aryl-1,2-mercaptoamines in water followed by monoamine oxidase (MAO-N) enzymatic resolution

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A facile microwave assisted three-component protocol allows the synthesis of chiral aryl-1,2-mercaptoamines in water in a few minutes with high yields, bypassing the use of toxic aziridine intermediates. The chiral 1,2-mercaptoamines were then deracemized through enzymatic resolution of the racemates using monoamine oxidase (MAO-N) biocatalysts.

1,2-Mercaptoamines, also referred to as β-aminothiols, are a class of organic compounds of wide interest that have found broad application in synthetic, pharmaceutical and material chemistry as well as in catalysis.[1] The uniqueness and versatility of these molecules resides in the presence of the two nucleophilic N and S heteroatoms and in their ability to chelate metals, making them ideal protein and metal ligands. The 1,2-mercaptoamine scaffold is present in naturally-occurring compounds such as the aminoacid cysteine 1, cysteamine 2, taurine 3 and the penicillin antibiotics such 4, and can be also found in commercially approved drugs like the antiretroviral agent nelfinavir 5, the ACE inhibitor zofenopril and the anticancer amifostine (Figure 1). Moreover, 1,2-mercaptoamine derivatives are commonly used in chemistry as precursors in the synthesis of a various *N,S*-heterocycles (e.g. thiazolines, thiazolidines, thiomorpholines, thiazepines)[1,2] or as ligands in organometallic catalysis.[3]

In view of their broad application, a number of synthetic methodologies to access 1,2-mercaptoamines has been described so far, such as the introduction of sulphur nucleophiles into α-amino acids or β-aminoalcohols,[4] the ring-opening of *N,S*-heterocycles[5] or the sulfenoamination of alkenes.[6] However, the most straightforward approach to 1,2-mercaptoamines remains the nucleophilic addition of a sulphur nucleophile to an aziridine ring A (Figure 1).[7] The ring opening reaction of aziridine substrates with thiols is generally carried out in the presence of stoichiometric amounts of Lewis acids ($BF_3{\cdot}Et_2O$),[7d,8] strong acids such TfOH[7e] or under basic conditions to generate the thiolate nucleophiles.[7a-c] Furthermore, thiols are often used in large excess (up to 20 eq)[7e] and the reactions require high temperatures and long reaction times to be completed.[9]

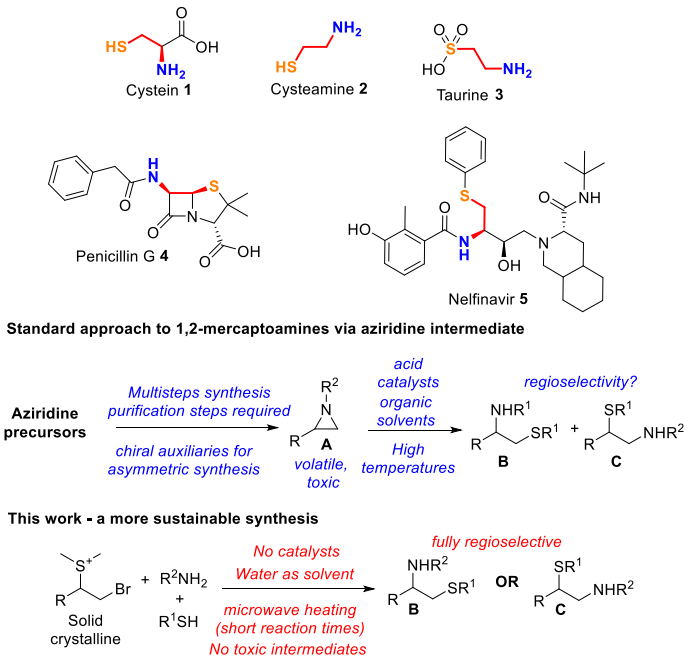

Figure 1. Examples of 1,2-mercaptoamines and this work's synthetic strategy

Catalytic $ZnCl_2$ was also found to promote the ring opening of aziridines bearing specific protecting groups on the nitrogen.[10] The aziridine ring-opening generally occurs on the less hindered carbon, but other factors such as the nature of the nucleophile or the substituents and the reaction conditions may affect the regioselectivity, leading to complex mixtures of regioisomers. A

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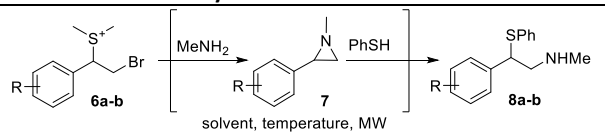
major limitation of these methods is represented by the use of the aziridine itself. In fact, the synthesis of aziridine intermediates can be a challenge, often requiring multiple steps, an appropriate protecting group strategy, the use of chiral auxiliaries in case of asymmetric syntheses,[11] or harsh reaction conditions.[11f] In addition, substituted aziridines can be carcinogenic[12] and mutagenic[13] due to their ability to bind DNA, and in general are highly irritant to eyes, skin and respiratory tract. All these factors, combined with their high volatility, make aziridines a major non-desirable hazard in chemistry laboratories.

As part of our studies aimed at the development of greener and more sustainable methods for the synthesis of sulphur derivatives and pharmaceutical scaffolds,[14] herein we describe a facile and regioselective microwave-assisted multicomponent protocol to generate chiral aryl-1,2-mercaptoamines like **B** or **C** (Figure 1). The desired β-aminothiols are synthesised directly from styrene sulfonium bromide (SBB), amines and thiols in 100% water, avoiding the use of acid/base catalysts and protecting groups as well as bypassing the formation and isolation of aziridine intermediates. To the best of our knowledge, this is the first regioselective multicomponent methodology for the synthesis of 1,2-mercaptoamines which does not involve the handling of aziridine intermediates. The methodology is selective to afford 1,2-mercaptoamines bearing a C-S stereocentre (compound **C**) with a few exceptions where a selectivity towards chiral amines **B** was observed.

Table 1. Optimisation of the reaction conditions for the one-pot microwave-mediated synthesis of aminothiols[a]



Entry	Product	Solvent	Time (min)	Temp. (°C)	Heating	Yield (%)[d]
1[b]		H_2O+DCM	18h+24h	30	Standard[c]	15[e]
2		DCM	15	60	MW	0
3		MeOH	15	60	MW	1-2
4		MeOH	20	60	MW	2
5		EtOH	15	60	MW	0
6	**8a**	Neat	15	80	MW	5[f]
7	R = H	H_2O	10	50	MW	12
8		H_2O	10	80	MW	25
9		H_2O	10	100	MW	18[f]
10		H_2O	10	150	MW	20[f]
11		H_2O	20	80	MW	39
12		H_2O	30	80	MW	79
13		H_2O	30	80	MW	10
14		H_2O	30	100	MW	25
15		H_2O	20	120	MW	40
16		H_2O	30	120	MW	40
17	**8b**	H_2O	10	150	MW	50
18	R = Cl	H_2O	20	150	MW	77
19		H_2O	30	150	MW	68
20		H_2O	20	160	MW	50
21		H_2O	30	160	MW	77

[a]The ratio of the reactants has been kept constant during the optimisation study with SBB (**5a-b**)/$MeNH_2$/PhSH = 1:10:1.1. Attempts to reduce the amount of amine led to poorer yields. [b]The reaction was carried out in two steps. Aziridine **6** was synthesised and the crude reacted with thiophenol. [c]The reaction was carried out in a water bath at 30 °C. [d]Isolated yields were reported. [e]Overall yield over two steps.[f]The formation of multiple side products was observed from the reaction mixture.

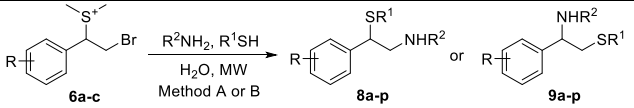
Finally, with the aim of making the protocol more sustainable, the deracemization of the chiral 1,2-mercaptoamines *via* enzymatic kinetic resolution or kinetic dynamic resolution with monoamine oxidase (MAO-N) biocatalysts was investigated. MAO-N enzymes have been widely studied as biocatalysts for the production of enantiomerically pure amines through the deracemization of a range of chiral substrates[15] and, more recently, have been exploited in the synthesis of nitrogen heterocycles.[14b-c] Turner and co-workers have mapped the substrate scope of MAO-N biocatalysts showing that these enzymes sometimes show poor enzymatic activity on non-cyclic amine substrates. However, no biocatalytic studies on 1,2-mercaptoamine derivatives bearing a C-S or a C-N stereocentre have been carried out to date.[16]

The reaction of crystalline SBB **6a**[17] with methylamine and thiophenol *via* a two-steps route was initially investigated. The SBB was reacted with an excess of methylamine at room temperature leading to the corresponding aziridine **7** in 18 h. The crude three-membered ring **7** was then opened by treatment with thiophenol in DCM for 24 h affording the 1,2-mercaptoamine **8a** as sole isomer in low yields (15%) (Table 1, *entry* 1). The disappointing yield, observed in triplicate experiments, was attributed to the volatility of the aziridine intermediate which was probably lost during the work up of the first reaction step. Surprisingly, only the isomer **8a** bearing a C-S stereocentre was formed, indicating that the thiophenol attacks the aziridine **7** on the most hindered benzylic carbon. The structure of **8a** was determined by NMR and on the basis of the literature data reported for similar compounds.[18] The ^{13}C NMR of **8a** presents a peak at 56.3 ppm compatible with a -CH_2-NHMe carbon and a peak at 51.3 ppm compatible with a -CH-SPh carbon. On the other hand, the -CH_2-SPh peak of β-aminothiols in ^{13}C NMR is expected to fall at around 40 ppm. In order to improve the yield of the reaction, the SBB, the methylamine and the thiophenol were then mixed in a one-pot multicomponent fashion. We reasoned that the SBB and the methylamine could react quickly leading to an aziridine intermediate which could be opened *in-situ* by the thiophenol. Moreover, we decided to perform the reaction under microwave irradiation to reduce the reaction times as well as the formation of potential side products. The SBB **6a**, methylamine and thiophenol were initially mixed in various solvents and irradiated under microwave at 60 °C. No significant formation of the aminothiol **8a** was observed in DCM, MeOH or EtOH, irrespective to the reaction time (Table 1, *entries 2-5*). A negligible yield was also obtained when the reaction was performed in neat (Table 1, *entry 6*). Surprisingly, when 100% water was used as solvent, an improvement in the reaction yield was observed after 15 minutes at 50 °C, with the formation of **8a** in 12% yield (Table 1, *entry 7*). The poor reactivity observed with organic solvents could be ascribable in part to the limited solubility of the sulfonium starting material. In addition, it has been reported that microwave irradiation can accelerate the reactions carried out in aqueous media and improve the reaction yields.[19] The increase of the temperature proved to be partially beneficial (Table 1, *entries 9-10*), while prolonged reaction times at 80 °C (30 minutes) led to **8a** in good 79% yield as single regioisomer (Table 1, *entry 12*). Attempts to

increase the reaction yield carrying out the multicomponent reaction at temperatures above 80 °C failed, probably due to the formation of by-products. Surprisingly, when the chloro-SBB substrate **6b** was used under the same reaction conditions, the corresponding 1,2-aminomercaptane **8b** was obtained only with 10% conversion (Table 1, *entry 13*). However, in this case, the increase in temperature proved to be beneficial (Table 1, *entries 14-17*) with **8b** was obtained in 77% yield when the reaction was carried out at 150 °C for 20 minutes (Table 1, *entry 18*). In this case, longer reaction times or higher temperatures did not affect the reaction yield. Also compound **8b** was obtained as a single regioisomer bearing a C-S stereocentre.

The scope of the multicomponent reaction was then explored. Since the reaction proved to be substrate specific, both Methods A (30 min at 80 °C) and B (20 min. at 150 °C) were applied to different substrates. The results and the best reaction conditions are reported in Table 2. With the exception of product **8a** and **8c**, obtained *via* Method A with 79% and 55% yields respectively, Method B proved to be the best in all the remaining cases. Excellent yields (71-83%) were obtained for aminothiols **8b**, **8d**, **8f-g** while derivatives **8i-k** and **8p** were recovered in good amounts (59-67%). Surprisingly, regioisomers **9e** and **9h** bearing a C-N stereocentre were obtained as single products using the same methodology. The regioselectivity of aziridine ring opening is often determined by a combination of multiple electronic and steric factors.[11e,20] It is plausible that in the case of **9e** and **9h** the inductive effects of the substituents on the thiophenols (Cl and Me) combined with the effect of the Cl-Ph substituent on the aziridine intermediate may have favoured the attack of the nucleophile on the less hindered carbon. When $EtNH_2$ and *i*$PrNH_2$ were used as reagents, β-aminothiols **8l-m** were obtained in good yields (59-46%). On the other hand, the reaction of **6a** with methylamine and aliphatic thiols (allylthiol and *n*-propylthiol) led to regioisomers **9n-o** bearing a C-N stereocentre.

Table 2. Substrate scope of the multicomponent synthesis of 1,2-mercaptoamines



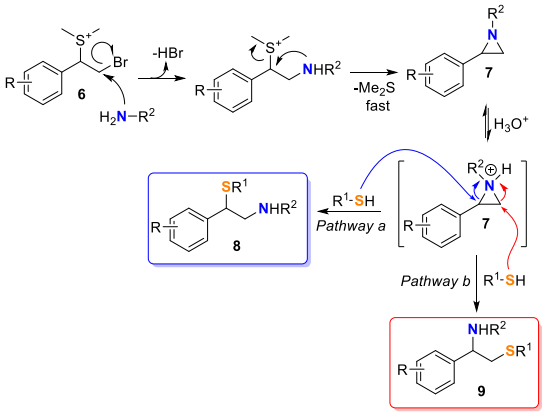
6a-c 8a-p 9a-p

	Method[a]	R	R^1	R^2	Yield (%)[b]
8a	A	H	Ph	Me	79
8b	B	Cl	Ph	Me	77
8c	A	Me	Ph	Me	55
8d	B	H	4-Me-Ph	Me	72
9e	B	Cl	4-Me-Ph	Me	44
8f	B	Me	4-Me-Ph	Me	80
8g	B	H	4-Cl-Ph	Me	83
9h	B	Cl	4-Cl-Ph	Me	71
8i	B	Me	4-Cl-Ph	Me	62
8j	B	H	4-Br-Ph	Me	57
8k	B	H	4-MeO	Me	57
8l	B	H	Ph	iPr	46
8m	B	H	Ph	Et	59
9n	B	H	Allyl	Me	42
9o	B	H	*n*Pr	Me	48
8p	B	H	Bn	Me	67

[a]Method A: H_2O, MW, 80 °C, 30 min. Method B: H_2O, MW, 150 °C, 20 min. [b]Isolated yields were reported

Also in this case, a nucleophilic attack at the less substituted carbon of aziridine **7** occurred, probably due to electronic factors.

A plausible mechanism for the multicomponent reaction is illustrated in Scheme 1. The primary amine undergoes a nucleophilic substitution on SBB **6** leading to a sulfonium amine intermediate with elimination of HBr. Then, the cyclic aziridine **7** forms spontaneously by ring closure and elimination of dimethyl sulphide. It is plausible that the aziridine ring is protonated in the reaction media (water). Two possible pathways are possible: in *pathway a*, the attack of the nucleophile occurs on the more hindered and electrophilic benzylic carbon, leading in most of the cases to regioisomers **8**. However, the nature of the nucleophiles and the reagents may affect the selectivity thus favouring the attack of the nucleophiles on the less hindered carbon and leading in a few cases to isomers **9** thorugh *pathway b*.[21]



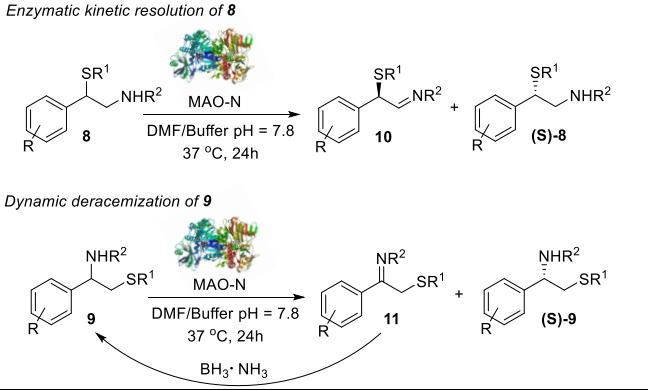
Scheme 1. Proposed mechanism for the multicomponent reaction

The enantioselective synthesis of chiral 1,2-mercaptoamine derivatives has proved to be a challenge to date, especially for derivatives bearing a C-S stereocentre, with only few methods described in the literature.[22,1a] In many cases, optically pure 1,2-mercaptoamines are generated from enantiopure amino acid precursors through multistep functionalization.[1] Herein, due to our previous experience in the biocatalytic synthesis of enantiomerically pure substrates,[14a,15] the enzymatic kinetic resolution of chiral compounds **8** using MAO-N as biocatalysts was investigated. Results are reported in Table 3.

The racemic amine **8a** was first treated with freeze-dried whole cells containing MAO-N variants D5, D9 and D11, selected on the basis of their known activity and selectivity towards primary and secondary amines.[16] All the enzymatic biotransformations were carried out at 37 °C in a buffer solution (pH = 7.8) using DMF as co-solvent according to standard protocols.[15] MAO-N are able to selectively oxidase one enantiomer into the corresponding imine **10** whilst leaving the other enantiomer unreacted. In the presence of MAO-N D9, amine **8a** was deracemized affording the enantiomer **(S)-8a** with 95:5 er (90% ee) (Table 3, *entry 2*). The absolute configuration was assumed on the basis of the known selectivity of MAO-N biocatalyst for *R*-enantiomers.[15] Attempts to isolate the imine **10** by LC-MS failed, probably due to its poor stability and hydrolysis. Poor er were

obtained when MAO-N D5 and D11 variants (Table 3, *entries 1 and 3*) were used. Good selectivity was observed for amines **8g** and **8p** (Table 3, *entry 7 and 12*), while almost racemic mixtures were recovered for other substrates. It is plausible that the C-S stereocentre could racemise during the course of biocatalytic transformation thus accounting for poor enantioselectivity.[23] Finally, a dynamic deracemization of derivatives **9n-o** bearing a C-N stereocentre was also attempted using MAO-N biocatalysts in the presence of $BH_3{\cdot}NH_3$ (*entries 10-11*). However, in this case, racemic mixtures of the amines were recovered.

Table 3. Biocatalysed deracemization of 1,2-mercaptoamines 8



Entry	Cmpd	Method[a]	Biocatalyst	Product	Yield (%)[b]	er[c] (ee%)
1			MAO-D5	**(S)-8a**	-	52.5:47.5 (5)
2	**8a**	EKR	MAO-D9	**(S)-8a**	55	95:5 (90)
3			MAO-D11	**(S)-8a**	-	63:37 (26)
4	**8b**	EKR	MAO-D9	**(S)-8b**	40	60.5:39.5 (21)
5	**8c**	EKR	MAO-D9	**(S)-8c**	18	67:33 (34)
6	**8d**	EKR	MAO-D9	**(S)-8d**	-	58:5:41.5 (17)
7	**8g**	EKR	MAO-D9	**(S)-8g**	52	77.5:22.5 (55)
8	**8k**	EKR	MAO-D9	**(S)-8k**	-	65:35 (30)
9	**8l**	EKR	MAO-D9	**(S)-8l**	-	64.5:35.5 (29)
10	**9n**	DD	MAO-D9	**(S)-9n**	52	51:49 (1)
11	**9o**	DD	MAO-D9	**(S)-9o**	68	53.5:46.5 (7)
12	**8p**	EKR	MAO-D9	**(S)-8p**	-	71.5:28.5 (43)

[a]EKR = enzymatic kinetic resolution; DD = dynamic deracemization. [b]Isolated yields were reported. [c]er = enantiomeric ratio. Determined by chiral LC-MS using a Chiralpak IG column

Conclusions

In conclusion, a green and sustainable approach to chiral aryl-1,2-mercaptoamines has been developed through a novel microwave-assisted multicomponent reaction carried out in water. The multicomponent reaction allows the regioselective synthesis of a variety of β-aminothiols **8a-p** bearing a C-S chiral stereocentre in short times and high yields, bypassing the use of toxic aziridine substrates and avoiding organic and chlorinated solvents as well as the purification of reaction intermediates. In a few cases, the 2-aryl-1,2-mercaptoamine regioisomers **9** were selectively obtained as single products. Finally, the deracemization of the chiral aryl-1,2-mercaptoamine derivatives with MAO-N biocatalysts was explored leading, in some cases, to enantioenriched compounds with high/good er. Additional studies on the biocatalytic synthesis of enantioenriched 1,2-mercaptoamines **8** are currently in progress in our laboratories.

Conflicts of interest

There are no conflicts to declare

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